Section II (Remarks)

A. Summary of Amendment to the Claims

By the present Amendment, claims 1, 8 and 20 have been amended; claims 4, 7, 18, and 21 have been cancelled; and new claims 30 - 35 have been added. Claims 5-6, 9, 16-17 were previously cancelled. No new matter within the meaning of 35 U.S.C. §132(a) has been introduced by the foregoing amendments.

The amendments made herein are fully consistent with and supported by the originally-filed disclosure of this application. Specifically, support for the amendment of claims 1 and 20, which further define the transport peptides as "cell penetrating" peptides, is found at page 4, paragraph 3. (See present application, pg. 4, ll. 17-19) Additionally, claims 1 and 20 have been amended to further characterize the peptide nucleic acid of the address module (AS), and to specifically identify the molecular target of the signalling module (SM). The additional amendments to claims 1 and 20 are supported at page 5, paragraph 3, and at page 6, paragraph 3, respectively. (See present application, pg. 5, ll. 17-29, and pg. 6, ll. 13-19)

New claims 30 – 35 have been added. Support for claims 30, 31, and 35, which recite the ions linked to the address molecule, is found at page 6, paragraph 3. (See present application, pg. 6, ll. 12-19) Support for new claims 32 – 34, which recite that the cell penetrating transport peptide is a transport peptide of human origin, is found at page 4, paragraph 4. (See present application, pg. 4, ll. 26-28)

B. Response to Rejection under 35 U.S.C. 112 First Paragraph- Written Description

Claims 1-4, 7-8, 10-15, and 18-29 were rejected in the Office Action mailed on October 9, 2007, under 35 U.S.C. 112 first paragraph, for failing to comply with the written description requirement. The Office Action maintains the rejection made in the previous Office Action mailed on April 2, 2007, that the claims contain subject matter not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventor, at the time the application was filed, had possession of the claimed invention. The applicants respectfully disagree.

Specifically, the Office Action states that the previously amended claim language, which limited the transport peptides of the present application to "transport peptide[s] capable of penetrating the plasma membrane," does not sufficiently describe the functional and structural characteristics of the transport peptides to place the claims in compliance with the written description requirement. (Office Action of October 9, 2007, pg. 4, ll. 11-14) The Office Action further states that "the instant claims encompass a genus of unidentified transmembrane peptides [cap]able [sic] of penetrating the plasma membrane" and that "[t]he disclosure of the specification is not deemed to be descriptive of the complete structure of the representative number of transmembrane peptides able to penetrate the plasma membrane…" (Office Action of October 9, 2007, pg. 4, ll. 20-21, pg. 5, ll. 1-5) Applicants traverse this rejection by the following remarks.

The examiner's attention is respectfully drawn to the following relevant law on the written description requirement of 35 U.S.C. § 112 first paragraph, as declared by the Federal Circuit.

> "The specification need not describe the claimed subject matter in exactly the same term[s] as used in the claims; it must simply indicate to persons skilled in the art that as of the [filing] date the applicant had invented what is now claimed." (emphasis added) *Eiselstein v. Frank*, 52, F.3d 1035, 1038, 34 USOQ2d 1467, 1470 (Fed. Cir. 1995).

More recently, with regard to the biochemical arts, the Federal Circuit has held that,

> "in accordance with our prior case law, (1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met ... even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." (emphasis added) *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006).

Additionally, the Federal Circuit has previously held that,

> "[a] claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation. (emphasis added) *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.* 424 F.3d 1336, 1345 [76 USPQ2d 1724] (Fed. Cir. 2005).

The Office argues that the claim language "transport peptide[s] capable of penetrating the plasma membrane" encompasses a genus of unidentified transmembrane peptides capable of penetrating activity that is too broad for one of ordinary skill in the in the art to envision, based only on the teaching in the present application and without undue experimentation. (Office Action of October 9, 2007, pg. 4, ll. 20-21, pg. 5, ll. 1-5)

As made clear by the above Federal Circuit line of cases, however, the written description requirement does not require that the specification contain examples covering the full scope of the claim language, but only that enough information is included in the claim language and in the specification to convey to one of skill in the art that the inventor possessed the invention at the time of filing.

Accordingly, the applicants have further defined the transmembrane peptides used for the transmembrane module by amending independent claims 1 and 20 to recite "the transmembrane module is a cell-penetrating transport peptide capable of penetrating the plasma membrane." (See present application, independent claims 1 and 20) Support for the claim amendments is found in the specification at page 4, paragraph 3. (See present application, pg. 4, ll. 17-26)

The transmembrane module that is a "cell-penetrating transport peptide capable of penetrating the plasma membrane" clearly defines a specific class of compounds well known by one of skill in the art, using terms that were well known by those of skill in the art at the time that the current application was filed. As evidenced by the review article of Maria Lindgren et al. ("Cell-penetrating peptides," *Trends in Pharmacological Science*, March 2000, Vol. 21, pp. 99-103; hereinafter "Exhibit A"), the term "cell-penetrating peptides" was used to identify a group of peptides capable of translocating across the plasma membrane by an energy-independent and receptor-independent mechanism, which also have the facility to deliver macromolecules conjugated thereto into a cell. (See Exhibit A, abstract) Further, Lindgren et al. provides evidence that several cell-penetrating peptide families including the analog sequences for these peptide families were also well known in the art at the time the present application was filed. (See Exhibit A, pg. 100, Table 2) As such, penetratin and transportan are examples for the class of cell-penetrating peptides that include signal-sequence-based peptides or amphiphilic model peptides. In addition, the article by Pooga et al. ("Cellular translocation of proteins by

transportan," *FASEB Journal* express article 10.1096/fj.00-078fje, published online April 18, 2001; cited in IDS as reference "AH"), the Lindgren et al. article ("Exhibit A"), and an article by Zhibao Mi et al. ("Characterization of a Class of Cationic Peptides Able to Facilitate Efficient Protein Transduction *in Vitro* and *in Vivo*," *Molecular Therapy*, Vol. 2(4), 2000; hereinafter "Exhibit B") all use the same exact terms to describe the same class of transport peptides. Therefore, those of skill in the art at the time the application was filed knew with specificity what kind of transport peptides are embraced by the expression "cell penetrating" transport peptides that are "capable of penetrating the plasma membrane."

Numerous members of the cell-penetrating transport peptides together with their transport capability for internalization of cargo-compounds into a cell were reported prior to the filing date of the application. Accordingly, the disclosure in the specification is sufficient to convey to one of skill in the art those transport peptides that are included by the expression "capable of penetrating the plasrna membrane." The examiner is respectfully reminded of the following, from MPEP 2163 section II., entitled **METHODOLOGY FOR DETERMINING THE ADEQUACY OF THE WRITTEN DESCRIPTION,**

> "there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

The functional description and examples within the application are more than specific enough to support the subject matter that is encompassed by the definition "cell-penetrating transport peptide capable of penetrating the plasma membrane," because this expression had a clear meaning in the art and, therefore, a person skilled in the art would readily know and appreciate which kind of transport peptides are embraced by such definition. (See e.g. MPEP § 2163, sec. II. (A) 3., "Determine Whether There is Sufficient Written Description to Inform a Skilled Artisan That Applicant was in Possession of the Claimed Invention as a Whole at the Time the Application Was Filed," and *In re Herschler*, 591 F.2d 693,697,200 USPQ 71 1, 714 (CCPA 1979). Since the expression "transport peptides which penetrate the plasma membrane" has a clear meaning in the art for a specific energy independent membrane translocating mechanism, the term does not comprise membrane proteins such as "mitochondrial carrier protein, ammonia transporters, Bacteriorhodopsin-like proteins including rhodopsin, transmembrane cytochrorne b-

like proteins, calcium ATPase transporter, Voltage gated ion channel and others" as argued by the examiner, because the latter membrane peptides do not translocate across the plasma membrane by membrane penetration via the same mechanism as the peptide constructs of the present application. (See Office Action mailed October 9, 2007, pg. 4, ll. 20-24, to pg. 5 ll. 1-2) This is evidenced by reference to Exhibit A, where it is pointed out that the art at the time the application was filed clearly distinguishes between the mechanism of "cell penetration" and other kinds of transport into the cell, such as endocytosis. (See Exhibit A, Lindgren et al., page 101, Box I)

The Office Action also contends that the structure and function relationship for the class of cell penetrating transport peptides has not been fully elucidated by those of skill in the art to adequately define this class of transport peptides. The Applicants disagree, and as support cite Derossi et al. (reference AH in the IDS) as well as the following references, which evidence the knowledge of one of skill in the art at the time the application was filed. Derossi et al. reports that more than 20 functional internalizing sequences were derived from Antennapedia third helix domain and refers to "other polypeptides which have been shown to be internalized." (See Derossi et al., at page 86, last paragraph) Further, Fischer et al. ("Structure-activity relationship of truncated and substitute analogues of the Intracellular delivery vector Penetratin," *Journal Peptide Research*, 2000, 55, 163-172; hereinafter "Exhibit D") have reported structure-activity relationship of truncated and substituted analogues of penetratin. (See Exhibit D, Abstract) Therefore, numerous cell-penetrating peptides of the penetratin family that are analogues of the Antennapedia third helix were known in the art at the time the current application was filed. Moreover, an additional article by Lindgren et al. (*Bioconjugate Chemistry*, 2000, vol. 11, pp. 619-626; hereinafter "Exhibit E") describing analogues of transportan and penetratin as well as the structure-function relationship, Soomets et al. (*Biochimica et Biophysica Acta*, 2000, Vol. 1467, pp.165-176; hereinafter "Exhibit F") further describing the analogues of transportan and the sequence structure necessary for the translocation property, Rojas et al. (*Nature Biotechnology*, 1998, Vol. 16, pp. 370-375; hereinafter "Exhibit G") discussing a signal peptide-based membrane translocating sequence, and Kilk et al. (*Bioconjugate Chemistry*, 2001, Vol. 12, pp. 911-916; hereinafter "Exhibit H") referring to a cell-penetrating homeodomain from another species (*Drosophilia*), all had reported numerous cell-penetrating peptides including variants and homologues of penetratin and transportan as well as discussions of the

structure-activity relationship of the peptide transduction domains prior to the filing date of the present application. (See generally Exhibits E, F, G, H) Therefore, as evidenced by the aforementioned Exhibits, the regions and domains of cell-penetrating peptides were well known in the art, established and easily available at the filing date of the application.

The Office Action also contends that the term "address module" as used by the applicants and defined in the specification does not "describe a genus of address modules other than SEQ ID No. 5 and the PNA sequences [cap]able {sic} of hybridizing with c-myc, c-ras, hern, sst1 or sst2 mRNA, in such full, clear, concise and exact terms so as to indicate that the Applicant[s] {sic} ha[ve] possession of these address modules at the time of filing the present application." (Office Action of Oct. 9, 2007, pg. 7, ll. 4-5) Accordingly, the applicants have amended claims 1 and 20 to limit the term "address module" in the claims to the subject matter that the examiner considers sufficiently supported by the specification. Therefore, the applicants respectfully request that the rejection be withdrawn in regard to the use of the term "address module," since the written description requirement is fully satisfied.

The Office Action further reiterates that the term "signalling module" fails to fulfill the written description requirement because "only one example is disclosed for the signaling module, the $Gd3^{+}$ -DTPH." (Office Action of Oct. 9, 2007, pg. 7, ll. 11-13) By the present amendment, the claims are limited to a compound trapping Gadolinium (Gd). Additionally, as is evidenced by Caravan et al., (*Chemical Review,* Vol. 99, pp. 2293-2352, 1999; hereinafter "Caravan") numerous Gadolinium complexes as well as conjugates were well known in the art prior to the filing date of the invention. (See Caravan, pp. 2295-2308) Therefore, the applicants respectfully request that this rejection be withdrawn in regard to the use of the term "signalling module," since the written description requirement is fully satisfied.

As discussed above, and as evidenced by Exhibits A and B, those of skill in the art at the time the application was filed fully knew and appreciated what kind of transport peptides are embraced by "cell penetrating" transport peptides that are "capable of penetrating the plasma membrane." Additionally, as discussed above and as evidenced by Exhibits D, E, F, G, and H, the structural and functional characteristics of the transport peptides as well as antisense PNAs capable of hybridizing to mRNA target sequences of tumor genes were well recognized in the art as of the

filing date. Further, the specification and claim language provides description of both the conjugate recited in the claims and its component parts. The claims as amended therefore satisfy the written description requirement of 35 U.S.C. § 112, first paragraph, and the applicants correspondingly respectfully request that this rejection be withdrawn.

C. Response to Rejection under 35 U.S.C. 112 First Paragraph – Scope of Enablement

Claims 1-4, 7-8, 10-15, and 18-29 were rejected in the Office Action mailed on October 9, 2007, under 35 U.S.C. 112 first paragraph, for failing to comply with the enablement requirement.

While the examiner admits that the specification is enabling for "[a] diagnostic conjugate for the molecular imaging of a human tumor expressing a c-myc, c-ras, hern, sst1 or sst2 gene comprising in sequential order: a tranmembrane transport peptide of SEQ ID NOs: 2, 3, or 4, conjugated via a cleavable linker to the [sic] a peptide nucleic acid which hybridizes with a c-myc, c-ras, hern, sst1 or sst2 mRNA, conjugated via a linker to a $Gd3^+$ complex, wherein said target specific antisense conjugated $Gd3^+$ transporter complex is transported across the cell membrane, wherein said hybrid is formed of said antisense peptide nucleic acid and the RNA target sequence, wherein said hybrid begins to be slowly enzymatically cleaved, thereby releasing the target specific antisense conjugated $Gd3^+$ transporter," the Office Action reiterates the rejection based on the assertion that the specification does not provide enablement for a more broadly claimed diagnostic conjugate. (Office Action of October 9, 2007, pg. 8, ll. 9-18) The applicants respectfully disagree and demonstrate in the following discussion that the specification is enabling for the subject matter of the amended claims.

The examiner's attention is respectfully directed to MPEP § 2163.08, Enablement Commensurate With the Scope of the Claims, which states,

> "[t]he Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is **well-known** is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art." (emphasis added) **MPEP § 2163.08**

Under the discussion of enablement in the Office Action mailed October 9, 2007, the Office repeats the reasoning that was made under the written description rejection, namely, that the claim language "transport peptide[s] capable of penetrating the plasma membrane" encompasses a genus of unidentified transmembrane peptides capable of penetrating activity, that is too broad for one of ordinary skill in the in the art to envision, based only on the teaching in the present application and without undue experimentation. (Office Action of October 9, 2007, pg. 9, ll. 16-20, pg. 5, ll. 1-5)

At the filing date of the application, those of skill in the art were aware of the transport peptides that are embraced by the expression "cell penetrating transport peptides which penetrate the plasma membrane," as including a group of peptides that translocate across the plasma membrane by an energy-independent and receptor-independent mechanism. Penetratin and transportan are illustrative of such known and well-established peptides. Numerous transport peptides of this group, as well as their capability to internalize various cargo-molecules into a cell, were reported in the various publications identified above. (See Exhibits A, B, D-H)

With respect to the "penetratin" and "transportan" variants, analogs and structure-activity relationships were reported that included the sequences responsible for the translocating capability. (See Exhibit A, E, the Lindgren et al. articles; Exhibit B, Soomets et al.; and Exhibit D, by Fischer et al.) Thus, from the broad knowledge of the structural sequences of these peptides that was well known in the art, and the well-established knowledge in the art at that time of the meaning and character of "transport peptides capable of penetrating the plasma membrane," a person skilled in the art is enabled to make conjugates according to the invention with a cell-penetrating transport peptide other than SEQ ID NOs: 2, 3 or 4, without any undue burden.

Since "transport peptides which penetrate the plasma membrane" were well-known in the art, and the structure-function relationships of these peptides were well known in the art at the time the application was filed, the invention of the present application is enabled to an extent that is commensurate with the scope of the amended claims. Considering that these transport peptides had reported regions and domains responsible for the cell-penetrating functionality that was well

known at the time the application was filed, a person skilled in the art could easily obtain the peptide sequences from a protein data bank without undue burden.

The Office Action has also rejected claims 1-4, 7-8, 10-15, and 18-29 for failing to comply with the enablement requirement of 35 U.S.C. § 112, with regard to the "address module" and the "signalling module." Accordingly, the applicants have amended claims 1 and 20 to limit the terms "address module" and "signalling module" in the claims to the subject matter that the examiner considers sufficiently supported and enabled by the specification. The applicants respectfully request that the rejection be withdrawn since the enablement requirement for the terms "address module" and "signalling module" is fully satisfied. Additionally, with regard to the "signalling module," the applicants note that the structure and synthesis of suitable Gd-complexes or Gd-conjugates are set out and readily obtainable from Caravan et al. without undue burden at the time the present application was filed.

D. Response to Rejection under 35 U.S.C. 102

Claims 1, 2, 4, 10, 12, 15, 18 and 19 were rejected by the Office Action mailed October 9, 2007 as being anticipated under 35 U.S.C. 102(e) by Collins et al., U.S. Patent Application Publication No. 2006/0074034, published on April 6, 2007 ("Collins"). The applicants traverse this rejection on the basis that Collins is not statutory prior art in regard to the present application.

The present application was filed under the provisions of 35 U.S.C. § 371 and claims the priority of International Patent Application No PCT/EP03/00609 filed January 22, 2003, which in turn claims priority to European Patent Application No. 02001506, which was filed on January 22, 2002. (See present application, pg. 2, ll. 4-6) Therefore, the earliest effective filing date of the claimed subject matter of the present application is the foreign priority date of January 22, 2002.

Collins was filed on September 17, 2002 and claims priority to provisional applications 60/322,86l, filed on Sep. 17, 2001 and 60/410,627, filed on September 13, 2002. Enclosed as Exhibit J is a copy of U.S. Provisional Application 60/322,86l. The Collins application disclosure, which is directed to the delivery of nucleic acids and analogs to a host to affect gene expression, does not relate in any cognizable manner to the disclosure of provisional application No. 60/322,861, which is directed to a plastic bottle in the shape of a football. Therefore, the

effective filing date of Collins is September 13, 2002, which is the filing date of the other provisional application to which Collins claims priority (U.S. Provisional Application No. 60/410,627). Accordingly, since the September 17, 2002 effective filing date of Collins is later than the earliest effective filing date of the present invention, which is January 22, 2002, Collins cannot be statutory prior art under 35 U.S.C. § 103(e) in regard to the present application. As such, the applicants respectfully request that this rejection be withdrawn.

E. Response to Rejection under 35 U.S.C. 103

The Office in the Office Action mailed October 9, 2007 rejected claims 1-7, 9, 15, 16, 18 and 19 as unpatentable over U.S. Patent No. 6,821,948 to Braun et al. ("Braun") in view of Caravan.

It is elemental law that in order for an invention to be obvious, the difference between the subject matter of the application and the prior art must be such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art. In order to meet this standard for a proper §103 rejection, all claim limitations must be disclosed or derivable from the cited combination of references, there must be a logical reason to combine the cited references to produce an operable combination and there must be a reasonable expectation of success. See MPEP §2143.

According to the recent U.S. Supreme Court decision in *KSR International Co. v. Teleflex Inc.,* 550 U.S._ , 127 S.Ct. 1727 (2007), the court did not disavow the previous "teaching, motivation, or suggestion" or "TSM" test, but stated that such TSM test *should not be strictly applied* in determining obviousness. In connection with this point the Supreme Court stated that:

> "A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently known in the prior art. … [Rather], it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant art to combine the [prior art] elements in the manner claimed." *KSR,* slip op. at 14.

In is fundamental to a proper rejection of claim under 35 U.S.C. § 103 that an examiner must provide a convincing line of reasoning supporting the rejection. **MPEP 2144** ("Sources of Rationale Supporting a Rejection Under 35 U.S.C. 103") citing *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985). The Supreme Court in *KSR* affirmed the validity of such approach, stating that "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."

As stated by the Supreme Court in *KSR,* and noted above, references that teach away from the invention are evidence of the non-obviousness of a claimed invention. The Court also reaffirmed that a fact finder judging patentability "should be aware…of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (*KSR,* slip op. at pp. 20-23)

The applicants traverse the rejection of claims 1-7, 9, 15, 16, 18 and 19 as unpatentable over Braun in view of Caravan, for the following reasons.

Braun in view of Caravan does not teach each and every limitation that is recited in the claims of the present application. Braun teaches a conjugate for the transport of an active substance into a cell. In example 4, Braun teaches a peptide conjugate construct for the transport of a peptide nucleic acid (PNA) into the cell that is "anti-sense with respect to the rat's P2 promoter c-myc." (Braun, col. 8, ln. 18) As evidenced by the above citation, Braun teaches a peptide conjugate complex for transport into the cell that is antisense with respect to the P2 promoter c-myc DNA, because it hybridizes with the P2 promoter that is not transcribed into mRNA. As such, Braun discloses a PNA that is antisense to a DNA but not a PNA that is antisense to an mRNA. Therefore, Braun does not teach or suggest an antisense PNA that hybridizes with an mRNA as is recited by the claims of the present application.

Additionally, Braun teaches way from the use of the diagnostic agents used in the present application. Braun refers to a plethora of "diagnostic agents" but does not contain any reference to agents that are used for magnetic resonance imaging (MRI). (Braun, col. 4, ll. 5-22) In fact, though Braun states that "the active substance may optionally be labelled, e.g. radioactively, with a dye, with biotin, avidin etc.," none of the labels that are exemplified are related to the contrast agents that are used in MRI. (Braun, col. 4, ll. 10-11) Further, Braun does not teach or suggest making a PNA conjugate that is antisense to the mRNA of an oncogene "selected from group consisting of c-myc, c-ras, hern-, sst1 or sst2" as is recited by the claims of the present application. (See present application, claims 1 and 21)

Additionally, Braun exemplifies peptides and nucleic acids as cargo molecules conjugated to a cell-penetrating transport peptide. Braun does not indicate that the use of metal chelates as suitable cargo molecules is possible. The lack of teaching in Braun in regard to metal chelates as cargo molecules conjugated to a cell-penetrating transport molecule is significant, since the chemical and physical properties of peptide or nucleic macromolecules conjugated to a cell penetrating peptide are very different from that of a metal chelate conjugated to a cell-penetrating peptide. Also, Braun does not teach or suggest a cell-penetrating transport peptide of human origin. All of the peptides disclosed by Braun are of synthetic construction.

The addition of Caravan to Braun does not overcome the deficiencies of Braun. The disclosure in Caravan is directed to a review of the uses of Gadolinium as a contrast agent. Caravan discloses that the "preparation of metal-chelate-dendrimer-antibody" constructs for use in imaging and radioimmunotherapy have been accomplished. (Caravan, pg. 2341, paragraph 2) Caravan also teaches that "[t]he challenge with regard to delivering sufficient quantities of paramagnetic label is substantial." (Caravan, pg. 2340, paragraph 3) The teaching of Caravan, however, is directed to the recognition of molecules on the surface of a cell. Caravan does not teach the cell-penetrating transport peptides according to the claimed subject matter of the present invention, which is a construct that is used to image the interior of the cell. The cell penetrating constructs of the present application do not recognize molecules on the surface of a cell, but directly interact: with the phospholipids of the membrane. (See Derossi et al., Figure 2) Therefore, the antibody or tissue-specific molecular constructs taught by Caravan are functionally distinguished from the cell penetrating constructs of the present invention. Moreover, Caravan teaches away from the present invention by stating that a gadolinium chelate complex is unlikely to enter cells due to its non-hydrophobic character. (Caravan, pg 2295, 2nd col., 1st paragraph) Accordingly, one of skill in the art would not be motivated to consider Braun in view of Caravan to make a conjugate for use in MRI.

Accordingly, considering that Braun et al. exemplifies only nucleic acids or peptide-like macromolecules to be conjugated to a cell-penetrating peptide and transported into a cell, and Caravan describes Gd-chelates that are largely physically and chemically different from nucleic acids or peptides, there is no apparent motivation for a person skilled in the art to combine these references. Additionally, Caravan teaches away from such combination of references, by

teaching that Gd-chelate complexes are unlikely to enter a cell due to their non-hydrophobic character. Therefore, the cell-penetrating construct claimed by the present application is not obvious in view of the combined teachings of Braun and Caravan. Accordingly, the applicants respectfully request that this rejection be withdrawn.

F. New Grounds for Rejection

Claims 18 and 21 were rejected in the Office Action mailed on October 9, 2007, under new grounds for rejection. By present amendment, claims 18 and 21 have been cancelled. Therefore, the rejection of claims 18 and 21 is moot, and the applicants respectfully request withdrawal of this rejection.

G. Fee Payable for Added Claims and Extension of Time

By the present Amendment, 6 new claims have been introduced and 4 claims have been cancelled, resulting in a net addition of 2 new claims being introduced, beyond the number for which payment was previously made. Small entity fees payable for such added claims are calculated as follows: $25.00 x 2 = **$50.00.**

The time for responding to the October 9, 2007 Office Action without extension was set at three months, or January 9, 2008. Applicants hereby request a 3 month extension of time under 37 CFR § 1.136 to extend the deadline for response to April 9, 2008.

Payment of the **$ 525.00** small entity fee specified in 37 CFR § 1.17(a) for a 3 month extension of time and **$50.00** for two new claims is being made via online credit card payment at the time of EFS submission of this response.

CONCLUSION

Based on the foregoing, all of Applicants' pending claims 1-3, 7-8, 10-15, and 18-29 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a Notice of Allowance. If any issues require further resolution, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

/steven j. hultquist/

Steven J. Hultquist
Reg. No. 28,021
Attorney for Applicants

INTELLECTUAL PROPERTY/
TECHNOLOGY LAW
Phone: (919) 419-9350
Fax: (919) 419-9354
Attorney File No.: 4121-171

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